REMARKS / ARGUMENTS

By the present amendment, claim 1 and claims dependent thereon have been amended to specify specific T cell lineages. Support for this amendment is found on page 33, lines 14-15 and 21-23; page 34, lines 7-10 and 24-29; page 35, lines 1-3 and 21-25; page 37 lines 2-7 and 16-20; page 42, lines 1-6 and 19-26; page 44, lines 9-16; and page 50, lines 21-24 of the application as filed. In addition, claims 18-21, 23, 25-28 and 44-49 have been canceled, rendering claims 1, 2, 4, 8, 10-17, 22 and 24 pending in the application. Contrary to the Examiner's statement on page 2, paragraph 2 of the Office Action, claim 24 has not been withdrawn.

The amendments to the claims have been made without prejudice and without acquiescing to any of the Examiners objections. Applicants reserve the right to pursue any of the deleted subject matter in a further divisional, continuation or continuation-in-part application. The amendment does not contain new matter and its entry is respectfully requested.

The Official Action dated March 28, 2006 has been carefully considered. It is believed that the amended specification and claims and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

35 USC§112, First Paragraph

The Examiner has objected to claims 1, 2, 4, 8, 10-17, 22 and 44-46 under 35 USC§112, first paragraph for failing to comply with the written description requirement. Specifically the Examiner has alleged that the amendment "wherein the T cells produced are not TCR-$\alpha\beta^{+}CD4^{+}CD8^{-}$ T cells" introduces new matter.

In order to facilitate allowance, claim 1 has been amended to incorporate the subject matter of claim 44. Specifically, claim 1 has been amended to specify particular T cell lineages including: $CD4^{-}$ $CD8^{-}$ $CD25^{+}$ $CD44^{+/-}$ double negative (DN) T cells; TCR-$\alpha\beta^{+}$

$CD4^+CD8^+$ double positive (DP) T cells; TCR-$\alpha\beta^+$ $CD4^-CD8^+$ T cells; and/or TCR-$\gamma\delta^+$ T cells. The phrase "not TCR-$\alpha\beta^+CD4^+CD8^-$ T cells" has been deleted, rendering this objection moot. Claims 2, 4, 8, 10-17 and 22 depend on claim 1 and thereby incorporate this amendment. Claims 44-46 have been canceled as being redundant.

In view of the foregoing, the Applicants respectfully request that all of the objections to the claims under 35 USC§112, first paragraph, be withdrawn.

35 USC §103(a)

The Examiner has objected to claims 1, 2, 4, 8, 12-15, 17, 22 and 44-46 as being obvious in light of Jaleco et al. (Jaleco et al. (2001) *J. Exp. Med.* 194:991-1001), Nakano et al. (Nakano et al. (1994) *Science* 265:5175), and Tatsumi et al. (Tatsumi et al. (1990) *Proc. Natl. Acad. Sci.* 87:2750-2754).

As mentioned above, claim 1 has been amended to specify specific T cell lineages, and claims 44-46 have been canceled. Claims 2, 4, 8, 12-15, 17 and 22 are dependent on claim 1 and therefore incorporate the aforementioned amendment. The Applicants respectfully traverse the rejection with respect to the amended claims.

The Applicants submit that the cited references fail to provide the necessary disclosure or motivation required to teach an *in vitro* system that supports T cell lymphopoiesis using OP9 cells modified to express Delta-like-1 or Delta-like-4, wherein the T cells produced include $CD4^-$ $CD8^-$ $CD25^+$ $CD44^{+/-}$ double negative (DN) T cells; TCR-$\alpha\beta^+$ $CD4^+CD8^+$ double positive (DP) T cells; TCR-$\alpha\beta^+$ $CD4^-CD8^+$ T cells; and/or TCR-$\gamma\delta^+$ T cells.

The Examiner has submitted that Jaleco et al. teaches that culturing HPCs with mouse S-17 stromal cells that express Delta-1 inhibits B cell differentiation and produces $CD3^+CD4^+$ $CD8^+$ T cells, and has submitted that the claims are obvious in light of this reference in combination with Nakano et al. and Tatsumi et al. The Applicants

respectfully disagree and submit that the *in vitro* system as claimed is notably different to the Jaleco et al. system in light of Nakano et al. and Tatsumi et al.

First, the *in vitro* system of the present invention is able to provide for the expansion of T cells, in particular T cells of the following lineages: $CD4^-$ $CD8^-$ $CD25^+$ $CD44^{+/-}$ double negative (DN) T cells; TCR-$\alpha\beta^+$ $CD4^+CD8^+$ double positive (DP) T cells; TCR-$\alpha\beta^+$ $CD4^-$ $CD8^+$ T cells; and/or TCR-$\gamma\delta^+$ T cells. The Applicants would like to direct the Examiner's attention to Example 2 of the application as filed. In this Example, the Applicants saw an increase in cellularity of 100 fold in the first week of culture and another 15-20 fold expansion by day 12. DP T cells accounted for the majority of the HPC-derived cells produced by day 12 (see Figure 3b-c of the application as filed). In contrast, Jaleco et al. observed considerably lower cellular expansion and the expansion reported was expansion of total cells. Jaleco et al. reported that the total number of cells expanded on Delta-1 expressing stromal cells was significantly lower than the total number of cells expanded on parental control stromal cells (8 versus 20 fold respectively). Hence, the use of Delta-1 expressing stromal cells reduced cellularity compared to control cells in this system. Further, Jaleco et al. did not disclose expansion of T cells within the first 12 days of culture. Instead, Jaleco et al. reported that total cells were increased 8 fold after 6 weeks of culture. Jaleco et al. did not assay and did not provide data regarding the increase in cellularity of CD4/CD8 positive T cells at two weeks of culture (Please see page 995 of Jaleco et al.).

Second, the Applicants respectfully disagree with the Examiner's statement on page 7 paragraph 5, that since claim 22 does not limit the invention to a particular range of expansion; "therefore the lower cellular expansion recognized by the applicant (Reply pg. 13, pgph 4) meets this limitation". As mentioned above, the cell expansion reported in Jaleco et al. is for total cells, and the expansion reported is negative in comparison to control cells. In contrast, the specification of the instant invention teaches "increased numbers of the T cell lineage", which refers to an increase in cells by at least about 10-

15 fold (page 6 lines 11-12). Hence, the Applicants respectfully submit that Jaleco et al. does not render the claims, including claim 22 obvious.

Finally, Tatsumi et al. did not report increased T cell numbers and Nakano et al. did not produce any T cells.

The Applicants respectfully submit that this unexpected advantage could not have been predicted in view of Jaleco et al. in combination with Tatsumi et al. and Nakano et al.

Further, the Applicants submit that a person skilled in the art would not be motivated to combine the Nakano et al. reference with the Jaleco et al. reference. The Examiner has alleged that Nakano et al. supplements the guidance of Jaleco et al. by teaching the use of mouse OP-9 stromal cells to generate lymphohematopoietic cells. However Nakano et al. disclose a system that provides for the differentiation of erythroid, myeloid and B cell lineages. The system does not provide for the differentiation of T cells. The Applicants would like to emphasis that the Nakano et al. system facilitates the generation of B cells, which are in fact the cell lineage that Jaleco et al. alleges to block with the expression of Delta-1 on S-17 cells. Thus, it would not be obvious to use the findings of Nakano et al., which discloses an opposing system, to facilitate the generation of T cells. The Applicants respectfully submit a person skilled in the art would not be motivated to combine the teachings of Nakano et al. with Jaleco et al., and thus would not be motivated to replace S-17 stromal cells with OP-9 cells.

The Applicants have noted the Examiner's suggestion that the obviousness rejection could be overcome by limiting the claims to a method of producing mature T cells. The Applicants agree that the cited art does not teach a method of producing mature T cells; however, the Applicants submit that this would be an excessive limitation of their invention. As mentioned above, the Applicants' *in vitro* system has unexpected advantages over the prior art. In addition, to being able to support the generation of mature T cells and T cells of other lineages, the *in vitro* system is capable of supporting

T cell expansion of these lineages. Further, reiterating the submission above, at a person skilled would not be motivated to combine the teachings of Nakano et al. with Jaleco et al., and thus would not be motivated to use OP-9 cells.

The Applicants respectfully submit that the current amendment overcomes the prior art and respectfully requests the rejection under 35 USC §103(a) be withdrawn.

The Commissioner is hereby authorized to charge any fee (including any claim fee) which may be required to our Deposit Account No. 02-2095.

In view of the foregoing comments and amendments, we respectfully submit that the application is in order for allowance and early indication of that effect is respectfully requested. Should the Examiner deem it beneficial to discuss the application in greater detail, he is kindly requested to contact the undersigned by telephone at (416) 957-1682 at his convenience.

Respectfully submitted,

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